INTRODUCTION TO GLOMERULAR DISEASES

Goals:

- **to explain the general mechanisms leading to glomerular diseases and**
- **to analyze what is known about their relationship to morphologic and clinical manifestations of glomerular injury**

Learning objectives

On completion of this lecture, the listeners should be able to:

1. Explain the pathogenesis of glomerular injury related to the formation of antigen-antibody complexes *in circulation*
2. Explain the pathogenesis of glomerular injury related to the formation of antigen-antibody complexes *in-situ*
3. Explain the pathogenesis of glomerular disease in injury by antibody directed against tissue antigens
4. explain the pathogenesis of glomerular disease in injury by abnormal activation of complement
5. Explain the impact of injury to visceral epithelial cells on glomerular filtration
6. Contrast and compare the different pathomechanisms of glomerular injury and explain how they may correlate with different patterns of glomerular injury and different clinical syndromes
7. Analyze mechanisms of podocyte injury in minimal change versus focal and segmental glomerular sclerosis
8. Identify the role of genetics in glomerular diseases in Alport syndrome and congenital nephrotic syndrome
9. Explain the concept of "risk alleles"
10. Explain the terms: glomerulonephritis, glomerulopathy, nephropathy, sclerosis

Additional resources:

- Robbins Basic Pathology, 10th edition, chapter 14, pages 550-555
- Review: Robbins Basic Pathology, 10th edition, chapter 3, pages 75-77, chapter 5, pages 134-136, 139-142
- Review – 1st year "Host Defense" course
- recorded urinary tract histology, part II (independent study)

OUTLINE

1. Kidney diseases in general and glomerular diseases – the context
2. Glomerular histology – brief review
3. Pathogenesis of glomerular diseases: immune complex-mediated versus other

4. Pathophysiology of immune complexes (refresher) and the concept of proximal versus distal zones

5. Circulating and in-situ immune complex mediated disease: postinfectious glomerulonephritis and membranous nephropathy
6. Anti- glomerular basement membrane-mediated glomerulonephritis, crescent formation
7. Abnormal activation of complement
8. Other mechanisms: podocyte injury – minimal change and focal and segmental glomerular sclerosis
9. Genetics and glomerular diseases: Alport syndrome and congenital nephrotic syndrome, "risk alleles"
10. Summary
11. vocabulary

Kidney diseases – the context

Each year in the US >100,000 people are diagnosed with end stage renal disease
CDC estimates that >10% of **adults** in the US (>20 million people) may have chronic kidney disease, of varying levels and seriousness
Causes of kidney failure can be classified as: - prerenal, - intrarenal, - postrenal
Glomerular diseases fit into a much bigger category of intra renal diseases and are actually much less common than diabetes and hypertension. However, their evaluation by biopsy plays a major role in the diagnosis and selection of therapies.

Histology review

Glomerulus consists of a glomerular tuft which is surrounded by a capsule (Bowman's capsule).
Glomerular tuft is composed of a network of capillaries which are lined by endothelium, held together by mesangium (consisting of cells & matrix) and surrounded by the basement membrane.
The latter separates the endocapillary space from the extracapillary space. In the extracapillary space, there are 2 types of epithelium: visceral (aka "podocytes"), which are anchored on the glomerular basement membrane and parietal epithelial cells, which line the inside of the glomerular capsule.
The glomerular cells can react to injury in different ways, including: phagocytosis (mesangial cells), proliferation (mesangial, endothelial, parietal epithelial); or they can sustain irreversible damage with subsequent depletion and scarring (podocytes). All of these processes may impact blood/primary filtrate flow.
Injury to glomerular basement membrane may lead to the loss of its structural integrity (with hematuria) or loss of selective filtering (with proteinuria) or, at times, both.

Pathogenesis of glomerular diseases

Many glomerular diseases are immune mechanism-mediated and can be caused by circulating or in-situ immune complex formation, by antibody against tissue antigen or by

abnormal activation of complement. To study these mechanisms, we need immuno stains (typically immunofluorescence on frozen sections) and electron microscopy.
Other mechanisms are less well studied/known and include soluble mediators and cells; nephron loss may lead to progression of kidney disease to end-stage disease.
The role of genetics in the pathogenesis of glomerular diseases is increasingly recognized and may include monogenic or polygenic diseases.

Pathology of circulating immune complexes
In systemic immune complex-mediated disease (type III hypersensitivity disease) there are 3 sequential phases in disease development Fig. 5-15, p.141

Phase I: formation of antigen-antibody complexes
Phase II: immune complex deposition, complement activation and leukocyte recruitment
Phase III: inflammatory reaction & tissue injury at the site of deposition, *vasculitis, glomerulonephritis, arthritis "innocent bystander" (or by "friendly fire") tissue injury*
Antibody has no specificity to glomerular components !!!
Complement activation and recruitment of leukocytes is a major pathway of antibody-initiated glomerular injury.

Pathophysiology of immune complexes and the concept of proximal versus distal zones

Formation of immune complexes does NOT ALWAYS lead to disease
The outcome of immune complex formation depends on several factors including factors impacting the following:
- pathophysiology of immune complexes
- duration of antigen exposure
- host response and
- localization of immune complexes in the glomerulus

Glomerular localization of antigen, antibody and immune complexes is influenced by their molecular charge and size.

The glomerular filtration barrier has 2 layers with negative charge. Highly cationic complexes become sub-epithelial while highly anionic complexes become sub-endothelial and those with neutral charge deposit in the mesangial matrix. Large complexes are cleared by the mononuclear phagocyte system and usually are not nephritogenic. However, if not cleared, they become sub-endothelial. Deposition of these proteins is also influenced by glomerular hemodynamics, mesangial function and the integrity of the charge-selective barrier.

Dynamics of immune complex formation:

- in antibody excess, large immune complexes are formed, which are rapidly phagocytized

- in slight antigen excess, small/intermediate immune complexes are formed, which bind less avidly to phagocytic cells and circulate longer
- in mononuclear phagocytic system overload (or intrinsic dysfunction) the immune complexes persist in circulation and there is a greater likelihood of their tissue deposition

The concept of the filtration barrier and distinction between the proximal and distal zones:
- immune complexes deposited in the proximal zones of the glomerular basement membrane (periendothelial space) elicit an inflammatory reaction in the glomerulus with infiltration of leukocytes and structural injury of the filtration barrier with hematuria
Simplistic explanation: these complexes are "seen" by the circulating inflammatory cells and hence elicit their reaction with injury and engagement (proliferation) of the endocapillary cells - mesangial and endothelial.
- antibodies directed to distal zones of the glomerular basement membrane (epithelium and subepithelium) form complexes in the distal zone and are largely non-inflammatory but affect podocytes (visceral epithelial cells) with alteration of the filtration barrier; they consequently cause proteinuria. The complexing of the antigen and antibody in the subepithelial space is unique because the binding occurs on the urinary side of the glomerular basement membrane. The site of the deposit is remote from the activators that are normally present in the circulation.
Simplistic explanation: these complexes are "not seen" by the circulating cells, hence there is no inflammatory reaction, no endothelial injury or mesangial engagement.

Immune complex-mediated glomerulonephritis:
- **circulating immune complex**
- **in-situ immune complex**

Circulating immune complex glomerulonephritis: postinfectious glomerulonephritis
- caused by trapping of circulating antigen-antibody complexes within glomeruli because of physio-chemical properties & hemodynamic factors peculiar to the glomerulus. Antibodies have **NO** immunological specificity for glomerular constituents
- antigens can be either exogenous (infectious) or endogenous (in autoimmune diseases such as Systemic Lupus Erythematosus)
- antigen-antibody complexes cause tissue damage by eliciting an inflammatory reaction at the site of deposition, i.e. the glomerular capillary wall

This is a type III hypersensitivity reaction; experimental model = serum sickness.

Deposition of immune complexes is associated with inflammatory reaction with influx of polymorphonuclear leukocytes (PMNs) which in turn lead to proliferation of the mesangial and endothelial cells, leading to progressive narrowing of glomerular

capillaries with diminished blood circulation (clinically accumulation of metabolic products with elevation of serum creatinine, i.e. renal failure; retention of water with edema and hypertension).
There is also STRUCTURAL damage to the integrity of the glomerular capillary wall with "Swiss cheese" holes. The latter leads mainly to hematuria with only some proteinuria.

Clinically, this process is manifested in the **NEPHRITIC SYNDROME**: hematuria, mild proteinuria, edema, renal failure, hypertension (HTN).

Kidney biopsy will show influx of PMNs and endocapillary (mesangial and endothelial) proliferation while immune complexes are detectable by immunofluorescence and electron microscopy. See also Lecture I.

What is the goal of the inflammatory response?
Degradation of immune complexes by neutrophils, monocytes/macrophages and mesangial cells leads to a healing phase, with complete resolution in most patients.

In-situ immune complex deposition with antigens on basal surface of epithelial cells: membranous nephritis
Reaction of antigen with an antibody on basal surface of epithelial cells causes injury to epithelial cells with foot process effacement and severe proteinuria.
Since the antibodies are directed to distal zones of the glomerular basement membrane (epithelium and subepithelium) this process is largely non-inflammatory and consequently there is NO cellular reaction.
As discussed above, the complexing of the antigen and antibody in the subepithelial space is unique, because the binding occurs on the urinary side of the glomerular basement membrane. The subsequent activation of complement and cytokine factors is modified, because the site of the deposit is remote from the activators that are normally present in the circulation. The reduced response produces a lesion that looks "benign" on light microscopy (i.e. no inflammatory cells, no endocapillary proliferation). The terminal complement membrane attack complex (C5b-9) is detected in urine because complement deposition and activation occurs in the urinary space after the immune complex has been formed.

Kidney biopsy shows:
- no inflammatory response – "no Swiss cheese" or "sieve" injury"
- subepithelial immune complex deposits are detectable by immunofluorescence and electron microscopy
- effacement of the epithelial cell foot processes is seen by electron microscopy

While immune complex subepithelial deposition impacts the filtration integrity of the epithelial cells and glomerular basement membrane, red blood cells are retained.

Clinically there is severe proteinuria but no hematuria. In humans this is associated with membranous nephropathy.

Membranous nephropathy can be reproduced experimentally in a model known as Heymann nephritis

- In this model rats are injected with antigen consisting of proximal tubular brush border. Animals develop antibodies against the brush border antigen. These antibodies also react with the basal surface of epithelial cells. Complement activation follows and shedding of the immune complexes from cell surface to sub-epithelial location occurs and granular sub-epithelial deposits are detectable by immunofluorescence (and electron microscopy). In humans this nephropathy is an autoimmune process. See also Lecture II.
- This type of antibody reaction can also occur with antigens planted along the epithelial aspect of the glomerular basement membrane such as viral, bacterial, drugs…

While this experimental model of membranous nephritis has been known since 1959, its validation was achieved only relatively recently (*NEJM, 2002, 346:2053*). This was possible following the discovery of several families with neonatal nephrotic syndrome and membranous nephropathy. Subsequent evaluation showed that mothers had mutations in neutral endopeptidase (NEP, normal podocyte antigen). NEP serves as pathogenic antigen in the podocyte cell membrane. Antibodies to this protein originate in women who genetically lack NEP because of truncating mutations in the *MME* gene coding for NEP. Immunization occurs during pregnancy when the mother's immune system is first exposed to NEP, strongly expressed by placental cells and by fetal cells, entering the mother's blood. From about the 18th week of gestation, maternal antibodies of the IgG class are actively transported across the placenta to the fetus, where they bind to the NEP antigen expressed on podocytes resulting in in-situ formation of immune complexes in the sub-epithelial space of the glomeruli in the kidney of the fetus. This activity results in damage to the glomerular basement membrane and the clinical findings of nephrotic syndrome in the newborn. These observations validated the in situ paradigm in human membranous nephropathy. Proteomic analysis of the target antigen in human "idiopathic" membranous nephropathy showed it to be the phospholipase A2 receptor (PLA2R) or thrombospondin type-1 domain containing 7A (THSD7A). It has been shown that most of the reactivity to PLA2R resides in the IgG4 subclass.

However, while our understanding of membranous nephropathy continues to evolve, it is apparent that this nephropathy does not fit well into the classification scheme of hypersensitivity diseases (i.e. it is neither a good example of type III nor of type II).

Moreover, the different pathways of glomerular injury (by circulating or in-situ immune complex formation) are not mutually exclusive and in humans more than one mechanism may contribute to injury. For example, in the case of postinfectious glomerulonephritis, in addition to glomerular injury caused by circulating immune complexes, there is also a component of in-situ immune complex deposition. The latter leads to the formation of

large subepithelial deposits, "humps" which are unique to postinfectious glomerulonephritis and therefore are diagnostically very useful.

Antibody directed against tissue antigens: anti-glomerular basement membrane glomerulonephritis

Anti-glomerular basement membrane antibody-mediated glomerulonephritis is an example of the type II hypersensitivity reaction, where the antigens are present on the cell surface or within the matrix (glomerular basement membrane), and there is direct injury to cells/matrix by an antibody-mediated process.
The deposition of antibodies in fixed tissues (such as glomerular basement membrane) activates complement and generates by-products (including chemotactic agents) that attract leukocytes (PMNs) and monocytes, which, together with anaphylatoxins C3a and C5a, increase vascular permeability. Leukocytes release a variety of pro-inflammatory substances, lysosomal enzymes, including proteases capable of digesting basement membrane (see Robbins, page 140, fig. 5.14).

Antibodies with specificity for glomerular basement membrane bind diffusely along its length as evidenced by linear stain for IgG seen by immunofluorescence (but not by electron microscopy). Antibody deposition causes severe damage to the glomerular basement membrane with extensive injury along its entire length similar to the "sieve effect". Since "holes" in this sieve-like injured basement membrane are big enough to let a large number of the red blood cells through, there is usually GROSS hematuria.
CLINICALLY: nephritic syndrome + RAPID renal failure aka:
RPGN, i.e. **R**apidly **P**rogressive **G**lomerulo**N**ephritis

Glomerular crescent:
In response to blood entering urinary space proliferation of the parietal epithelial cells occurs which forms a crescent-shaped structure, which obliterates entry to the proximal tubule. Glomerular crescent prevents bleeding into the lower urinary tract and hence acts like a "glomerular stopper". The thereby-achieved control of blood loss comes at a price: crescents stop blood loss via the lower urinary tract but also compress the tuft, reduce filtration and lead to rapidly progressing renal failure.

The experimental model known as "Masugi nephritis" provides an insight into what happens in humans. In this model, rats are injected with anti-rat kidney antibodies (prepared in rabbits) with linear deposition of the antibody (IgG) along the glomerular basement membrane. In humans, the antigen involved in this process has been identified as a noncollagenous domain (NC1) of the α3 chain of collagen type IV, which, under normal circumstances, is encrypted and does not elicit an autoimmune response. See also Lecture I. Interestingly, these antibodies also cross-react with alveolar basement membrane in the lung, causing pulmonary hemorrhage, and the combination of this type of kidney and lung injury is known as Goodpasture syndrome.

Glomerular diseases can also be caused by complement activation in the absence of antibody:
Unregulated/excessive activation of the alternative complement pathway may lead to complement-mediated injury. During such an event, there is a transformation from low-grade physiologic complement activity ("tick-over") to unrestrained hyperactivity with tissue damage.
Excessive complement activation may be triggered by minor vascular injuries in individuals with either acquired autoantibodies against complement components or with inherited abnormalities of complement regulatory proteins.
Examples of such diseases in humans include glomerular dense deposit disease/C3 glomerulonephritis and thrombotic microangiopathies which are part of systemic diseases with significant renal manifestations; see also Lecture III

Complement system (Robbins, pp 75-77)
Components of the complement system (labelled C1-C9) are present in plasma in inactive forms. When activated by proteolysis complement components acquire their own proteolytic activity, thus setting up enzymatic cascade
There are 3 initiating pathways:
- classical: triggered by antibody [IgG, IgM] bound to antigen (humoral immunity)
- lectin: mannose-binding lectin (MBL) (innate immunity) - binding lectin to the mannose surface of pathogenic bacteria (both classical & lectin pathways begin with engagement of early complement components)
- alternative pathway (innate immunity) begins @ C3 and is *constitutively active*
All 3 pathways converge at C3 to generate **C3 convertase** that cleaves C3 into C3a and C3b; C3b + convertase ultimately generates C5 convertase which cleaves C5 & triggers the terminal complement cascade (C5b, C6, C7, C8, C9) and their regulators & assembly of membrane attack complex and cell lysis.

C3 convertase is tightly regulated by factors which can quickly degrade it (factor H).

Mutations in gene encoding factor H, development of autoantibodies to factor H or factor H deficiency will lead to decreased C3 convertase degradation with sustained activation of the alternative complement pathway. Similar effect can be achieved by the action of C3NeF(C3 nephritic factor), an autoantibody against C3 convertase, which binds to C3 convertase & prevents its degradation (stabilizes it) causing sustained complement activation and secondary C3 depletion in plasma.

Summary: the alternative pathway of complement is a powerful and evolutionarily old defense system of innate immunity that recognizes and destroys invading infectious microbes and also targets and eliminates modified self cells. Alternative pathway is a spontaneous self□amplifying initiator of complement.

Immune mechanisms causing glomerular injury - summary comments:

Immune complexes can form in circulation or in-situ.

In glomerulonephritis caused by circulating immune complexes, antibodies have NO immunological specificity for glomerular constituents

In in-situ immune complex deposition, antibodies have immunological specificity for glomerular constituents, which can be either fixed intrinsic tissue antigens (autoimmunity) or planted antigens (exogenous or endogenous).

In the case of antibody directed against tissue antigens, anti-glomerular basement membrane antibody binds *diffusely* along the glomerular basement membrane (linear stain for IgG [antibody]) with severe damage to the glomerular basement membrane, with GROSS hematuria; there is formation of crescents and a clinical picture of rapidly progressive glomerulonephritis.

Glomerular (and systemic vascular injury) may also be caused by excessive complement activation in the absence of antibody.

The type of glomerular response to injury and the clinical picture are largely dependent on the localization of the immune complexes in the glomeruli:

- endothelial/sub-endothelial antibodies/complexes – inflammatory reaction
- epithelial/sub-epithelial antibodies/complexes – non-inflammatory reaction

Inflammatory injury is clinically associated with hematuria and NEPHR**I**TIC syndrome

Non-inflammatory injury is clinically associated with proteinuria and NEPHR**O**TIC syndrome. However, other mechanisms (non-immune complex mediated) of glomerular injury can also lead to proteinuria and nephrotic syndrome as discussed below.

Other mechanisms of glomerular injury – NOT caused by detectable antibodies – podocyte injury: minimal change disease, focal and segmental glomerular sclerosis (FSGS)

Other mechanisms of glomerular injury where we do NOT detect antibodies by standard techniques (immunofluorescence, electron microscopy) and which are ***less well known*** include the following mediators:

- cells: neutrophils, monocytes, macrophages, resident glomerular cells T lymphocytes, NK cells, platelets,
- soluble mediators: complement, eicosanoids, NO (nitric oxide), angiotensin, endothelin, cytokines, chemokines (PDGF [Platelet-derived growth factor] induces proliferation, TGF-β [Transforming growth factor-beta] induces the synthesis of various extracellular matrix proteins), coagulation system

HEAVY PROTEINURIA/NEPHROTIC SYNDROME can develop following isolated injury to visceral epithelial cells (podocytes) by:

- putative antibodies to podocytes: cytokines ? or a not-yet-characterized "permeability factor", which may cause recurrence of proteinuria post kidney transplantation
- injury to podocytes may be reversible or seemingly irreversible. In this context, one should remember that mature podocytes do NOT proliferate; hence, irreversible podocyte injury leads to scarring

Among the various experimental models of epithelial cell injury are those involving toxins (puromycin) or hyperfiltration (partial nephrectomy)

Pathology of podocyte injury:

- reversible, manifested by effacement of the epithelial cell foot processes (minimal change disease)
- irreversible, associated with podocyte detachment, death and progressive obliteration of the affected capillary termed "sclerosis"(focal and segmental glomerular sclerosis)
- podocyte injury is also associated with alteration of the glomerular basement membrane charge with loss of its negative charge and, consequently, its permeability to negatively charged proteins such as albumin with severe proteinuria.

It is not clear whether minimal change disease and FSGS represent one disease (but at opposite ends of a spectrum) or two different diseases.

Podocyte injury (podocytopathies) leads to heavy proteinuria, which is the hallmark of NEPHROTIC syndrome. You may recall that nephrotic syndrome can also be caused by subepithelial immune complex deposition.

Nephron loss
Once renal disease, glomerular or otherwise, destroys sufficient nephrons to reduce the glomerular filtration rate to 30-50% of normal, progression to end stage renal disease proceeds at varying rates via scarring, called glomerulosclerosis
Adaptive changes in response to the loss of nephrons at this stage are ultimately maladaptive and exacerbate progressive sclerosis

Genetic defects:
(i) monogenic
(ii) polygenic aka "risk alleles"
Mutations in genes (monogenic) encoding:
- type IV collagen with hematuria (Alport syndrome)
- slit diaphragm proteins with nephrotic syndrome: *NPHS1* encoding *nephrin* – congenital nephrotic syndrome of the Finnish type, *NPHS2* encoding *podocin* – steroid-resistant nephrotic syndrome of childhood onset

Development of high throughput technologies has opened up the opportunities for studying polygenic diseases.

GWAS [genome-wide association studies] have been instrumental in the identification of the genetic component in polygenic diseases.

GWAS searches the *entire* genome for small variations, single nucleotide polymorphisms or SNPs ("snips") that occur more frequently in people with a particular disease than in people without the disease. Thus, each study can look at hundreds or thousands of SNPs at the same time to pinpoint genes that may contribute to a person's risk of developing a certain disease, "risk alleles". Several common diseases in which many genetic variations contribute to a person's risk, and which were identified by GWAS, include diabetes, heart abnormalities, Parkinson's disease, Crohn's disease, hypertension…
It is hoped that, in the future, more SNPs associated with chronic diseases, and variations that affect a person's response to certain drugs or influence interactions between a person's genes and the environment, etc can be identified and thereby facilitate a truly "personalized medicine".

To this end, recent studies have shown that genetic variants in the APOL1 gene account for a large fraction of the high rates of nondiabetic kidney disease in African Americans

APOL1 risk variants have large effects on several different types of kidney disease previously thought to be distinct entities: **FSGS [Focal and Segmental Glomerular Sclerosis], HIV-associated nephropathy, severe lupus nephritis, sickle cell nephropathy and unspecified chronic kidney disease**, often previously labelled as "hypertensive nephropathy in African Americans"

These variants, found only in individuals with recent African ancestry, (<10,000 years) confer enhanced innate immunity against African trypanosomes. These alleles are nearly absent in populations of European and Asian ancestry

APOL1 risk variants arose approximately 4,000 years ago in Africa and rose quickly to high frequency. In Nigeria, approximately 46% of chromosomes contain either the G1 or G2 allele. The ancestors of modern Europeans left Africa many millennia before the origin of these risk alleles, so the risk alleles are not found in Europeans. Today, approximately 36% of all African Americans carry the G1 or G2 alleles.
People who have at least 1 copy of either the G1 or G2 variant are resistant to infection by trypanosomes (protozoa), but people who have 2 copies of either variant are at an increased risk of developing a non-diabetic kidney disease. Genotype may be G1/G1, G2/G2, or the compound heterozygous state of G1/G2

The presence of the alleles is not enough to have the phenotype. These are risk alleles rather than single-gene disorders and additional "hits" are necessary, which may be genetic, environmental, or both. This, however, provides an opportunity for the development of preventive measures for those at risk.

Lessons learned from these studies indicate that:

- genetic differences substantially influence an individual's lifetime risk for kidney disease
- evolution of genes related to host defense against pathogens may limit kidney longevity
- expanding our understanding of renal development and function may enable the design of novel therapeutics for kidney disease as well as preventive measures for those at risk

The variants have proven to be useful for genetic screening in African Americans and in the selection of kidney donors

GWAS studies have also identified a genetic component in IgA nephropathy. Geographic and racial differences in the prevalence of IgA nephropathy have long been recognized and, until recently, it was still debated to what degree these were due to differences in disease diagnosis (e.g., due to diverse local biopsy practices) rather than biology. However, it is now clear that a substantial portion of disease risk is conferred genetically. A recent series of genome-wide association studies have identified at least 7 susceptibility loci in IgA nephropathy. The genetic loci identified thus far comprise genes associated with innate and adaptive immunity, and the complement system. Interestingly, the complement locus involve genes encoding proteins that regulate the alternative complement pathway.

Pathogenesis - summary:
(i) NEPHRITIC SYNDROME - **HEMATURIA**

- circulating immune complexes **– postinfectious glomerulonephritis** (serum sickness model)
- anti-glomerular basement membrane antibody mediated
  GROSS hematuria/rapidly progressing renal failure –
  anti-glomerular basement membrane disease (nephrotoxic serum [Masugi] nephritis)

(ii) NEPHROTIC SYNDROME – **PROTEINURIA**

- in-situ immune complex formation **– membranous glomerulonephritis** (Heymann nephritis model)
- podocyte injury non-immune complex mediated
  reversible = **minimal change disease**
  irreversible = **focal and segmental glomerular sclerosis (FSGS)**

Genetics: monogenic and polygenic diseases with defects affecting (i) glomerular structure or (ii) immune response

Different pathways of glomerular injury are not mutually exclusive and in humans more than one mechanism may contribute to injury.

Host factors, which usually are not static, are also critical in determining who does, and who does not, develop glomerular disease.

Thus, the disease is a dynamic process, more akin to a movie rather than a snap-shot

During the subsequent lectures, I will discuss the specific clinical entities associated with nephritic syndrome (Lectures I and II) and nephrotic syndrome (Lectures II and III).

VOCABULARY

Glomerular diseases usually have the **"glomerulo"** prefix: – see postinfectious glomerulonephritis etc

Glomerulonephritis is used preferentially in reference to glomerular diseases with an inflammatory/proliferative response

Glomerular pathologies, without an inflammatory response may be referred to as "nephropathy"or "glomerulopathy" - see membranous nephropathy (glomerulopathy)

Nephrosis is meant to indicate a non-inflammatory nephropathy, which is associated with nephrotic syndrome

"nephritis" can also be attached/used in connection with other kidney diseases, such as "pyelonephritis"

Greek: nephros = kidney, nephrologist = MD specializing in medical kidney diseases
Urologist takes care of "surgical "kidney diseases such as tumors, reflux, etc.

Sclerosis: σκληρός sklirós [Greek] = hard

Glomerular sclerosis: increased collagenous extracellular matrix that is expanding the mesangium, and subsequently obliterating the capillary lumen, or forming adhesions with the Bowman's capsule

Vascular sclerosis:

Hyaline arteriolosclerosis: hyaline (proteinaceous) deposits with thickening of the wall and narrowing of the lumen of small arteries, i.e."arterioles"

Hyaline from Greek: *crystal, glass*. A hyaline substance appears glassy and pink in H&E stain

Arteriosclerosis: "hardening of the arteries", wall thickening and loss of elasticity

Nephrosclerosis: "hardening" of the kidney due to vascular disease

H&E stain (hematoxylin & eosin stain) = routine pathology stain in which cytoplasm is pink (owing to staining with eosin) and nuclei dark blue (owing to staining with hematoxylin)